

## ABSTRACT

The invention is directed to modified blood clotting factors, such as Factor VII, that have a proteolytic cleavage site engineered into them. Various proteolytic cleavage sites, such as PACE/furin sites and others recognized by proteases of the mammalian protein transport pathway (i.e., endoplasmic reticulum-golgi) can be used in the modified blood clotting factors of the invention. Expressing modified blood clotting factor in a cell having the protease results in cleavage at the cleavage site thereby activating the protein (e.g., Factor VII is activated to Factor VIIa). Nucleic acids encoding modified blood clotting factors of the invention can be introduced into cells of the body using gene therapy protocols described, for example, in U.S. application serial No. 09/038,910, which is incorporated herein by reference. Secretion of cleaved/activated blood clotting factor (e.g., Factor VIIa) by the cells into the blood stream, for example, can ameliorate some or all of the pathological disorders or symptoms associated with a blood clotting or bleeding disorder in a subject. Therefore, invention modified blood clotting factors and nucleic acids encoding such modified factors are useful in treating hemophilia and other disorders. Hemophilia B subjects that express serum Factor IX after employing an AAV gene therapy protocol is described, for example, in Kay et al., Nat. Genet. 24:257 (2000), which is incorporated herein by reference.

## II. INVENTION DESCRIPTION

*Describe invention completely, addressing each of the following questions. Sketches, drawings, photographs, and any pertinent manuscript should be attached to this disclosure. Manuscripts which address questions 1-3 below are acceptable substitutes for Section II.*

1. What is the purpose and object of the invention in general terms? *(Is the invention a new process, composition of matter, device, or one or more products? A new use for or an improvement to an existing product or process?)*

The purpose of this invention is to describe a novel gene therapy approach for the treatment of hemophilia (A or B) or other bleeding disorders using a suitable gene delivery vector (for example, but not limited to, adeno-associated virus vector (AAV)) expressing activated human factor FVII (FVIIa). This can initiate coagulation in individuals who lack intrinsic pathway proteins, have inhibitors to these proteins, or who have some other hemostatic abnormality which would benefit by administration of coagulation factor VIIa.

Experience with recombinant factor VIIa protein has shown that it provides excellent hemostasis in individuals with hemophilia who have developed